The Amount of Circumscribed Brain Edema and the Degree of Post-Ischemic Neuronal Recovery do not Correlate Well

JOHN M. HALLENBECK, M.D., D. R. LEITCH, M.B., PH.D., A. J. DUTKA, M.D., AND L. J. GREENBAUM, JR., PH.D.

SUMMARY Fifty-four dogs were exposed to multi-focal ischemia sufficient to maintain suppression of the \( P_{1} - N_{1} \) amplitude of the cortical sensory-evoked response (CSER) for 60 minutes. Subsequently, the \( P_{1} - N_{1} \) amplitude recovery of the CSER was followed for an additional 15, 60, or 120 min while the dogs were treated or left untreated. The combination of PGI\(_2\), indomethacin, and heparin promoted a statistically significant augmentation of CSER amplitude return relative to: 1) no treatment; 2) PGI\(_2\) alone; 3) indomethacin alone; 4) PGI\(_2\) and heparin; 5) indomethacin and heparin; 6) PGI\(_2\) and indomethacin. Percentage gray matter water by the wet weight/dry weight technique was significantly elevated in all embolized groups compared to ten non-embolized controls, but the percentage recovery of the CSER did not correlate with the presence or degree of gray matter edema among embolized animals followed for 1 hour. Separation of embolized animals by the presence or absence of “neuron-disabling” flows (defined as 0-15 ml/100 gm/min for gray matter and 0-6 ml/100 gm/min for white matter) did produce significantly different mean CSER percentage recoveries but percentage gray matter water in the two groups was comparable. A proposed explanation of the data is that brain ischemia engenders two parallel processes which may become uncoupled. Ischemia creates metabolic conditions that lead to increased cellular inhibition of water and produces increased vascular leakiness. These perturbations increase brain water content. Concomitantly, there is an occurrence of further metabolic derangements and a multifactorial interaction at the blood-endothelial interface which have a direct influence on neuronal function and recovery.

EXTENSIVE STUDY in a variety of experimental models has established that brain ischemia leads to brain edema, an increase in brain tissue volume due to an increase in its water content.\(^1\,\,2\) When the edema is massive, as in large cerebral infarctions, it can cause severe intracranial hypertension and brain herniation at several sites.\(^3\) Under these circumstances, the contribution of increased tissue fluid to brain damage and dysfunction would seem straightforward and unequivocal. When clinical deterioration follows a cerebrovascular ischemic event, it is common practice to invoke the development of brain edema as a probable explanation. However, when the edema is circumscribed rather than massive, its potential for increasing neuronal injury and hindering recovery is less clear. Although this form of fluid accumulation would increase local tissue pressure with a corresponding decrease in local perfusion pressure and could increase cell-capillary separation with a consequent increase in oxygen diffusion distances,\(^4\) the effect of circumscribed edema on neuronal function and recovery remains a subject for experimental inquiry.\(^5\) The results of the present studies demonstrate that, in a model of reversible, multifocal ischemia, neither the presence nor amount of circumscribed edema is a good predictor of the degree of post-ischemic neuronal recovery as indicated by the cortical sensory-evoked response (CSER). Brain waters were measured as one aspect of a study designed to test the therapeutic efficacy of PGI\(_2\), indomethacin, and heparin in reversible cerebral ischemia.\(^6\)

Methods

Sixty-four conditioned male mongrel dogs weighing between 8.1 and 16.4 kg were entered into the experimental protocol (54 embolized; 4 brain water controls prepared but not embolized; 6 brain water controls not exposed to surgery). After sedation with xylazine 1.1 mg/kg and atropine 0.05 mg/kg subcutaneously, anesthesia was induced by alpha-chloralose (80 mg/kg) administered intravenously with incremental doses as needed. The animals were intubated and mechanically ventilated. End-tidal PCO\(_2\) and PO\(_2\) were continuously monitored by Beckman LB-2 and OM-11 analyzers. Rectal temperature was maintained at 37-38°C with heating pads and infrared light. Two catheters were placed in the right femoral artery. One was directed proximally into the aorta and the other was inserted into the distal femoral artery. The proximal catheter permitted sampling of arterial blood. When the two catheters were later joined through a Y-connector, the arterial flow to the leg was externalized, permitting rapid sampling of arterial blood for the \(^{14}\)C-iodoantipyrine autoradiographic blood flow assay.\(^7\) A catheter was threaded into the aorta from the left femoral artery, and two catheters were placed in the left femoral vein. One venous catheter was advanced into the inferior vena cava for infusion of solutions, sampling of venous blood, and infusion of isotope during the blood flow study. The other venous catheter was advanced into the right ventricle and permitted rapid injection of a solution of saturated potassium chloride to terminate the blood flow study. The arterial catheter was connected to a strain gauge for monitoring of arterial blood flow.
pressure. Polyethylene catheters were placed percutaneously into the cephalic vein of each foreleg as routes for administration of i.v. solutions. The right internal carotid artery was exposed and catheterized with PE 50 tubing. A lead II electrocardiogram was connected for monitoring heart rate and rhythm.

The dogs were placed in a Kopf® stereotaxic apparatus. Stainless steel screw electrodes were inserted into the skull. The recording electrode was positioned over the right sensorimotor cortex and the reference electrode was embedded in the nasal bones at their distal extreme. Electrode impedances were less than 3 kohms. Stimulating electrodes were positioned in the left upper foreleg such that the median nerve was included between them. A square wave stimulus of 300 μs sec duration at a rate of 1.1/sec was led through a Grass photoelectric stimulus isolation unit with constant current output (Model PISU6C) to the stimulating electrodes. The strength of the stimulus was adjusted to cause a maximal cortical sensory-evoked response (CSER) over the contralateral somatosensory cortex. Potentials from the recording electrodes were initially led to a Nicolet HGA-100 preamplifier with a 0.25 Hz to 10 kHz band width and a 10⁴ gain. The output was led to a Nicolet 1073 computer of average transients (CAT) and displayed on a Tektronics 5110 oscilloscope. The CAT output was recorded on a Hewlett-Packard 7045A XY-plotter.

As a final preparatory step, a needle was inserted by percutaneous puncture into the cisterna magna for measurement of the cerebrospinal fluid pressure.

After each animal was prepared, a series of not less than five CSER’s were recorded as a baseline. The latency of the first positive peak, P₁, was noted and all recorded amplitudes from P₁ to N₁, the first negative peak, were averaged to yield a control value.

Following these baseline measurements, 30–50 μl of room air was injected as a bolus into the right inter nal carotid artery catheter and flushed in with 500 μl of saline. After 2 min, another CSER was recorded. If the response was suppressed to between 10 and 20% of the control amplitude, no more air was infused. If the CSER was only partially suppressed, another 20–50 μl of air was delivered. This sequence was repeated until the CSER amplitude was 10–20% of the control value. Suppression of the CSER to values less than 10% of control was avoided. An animal was not eligible for inclusion in the series if it took longer than 10 min to achieve the initial suppression. Subsequently, the periodic regrowth of the CSER to values of 20% of control or greater was suppressed to a level between 10 and 20% of control by periodic infusion of 20–50 μl of air. The volume of these incremental infusions of air was determined by the apparent sensitivity of the evoked response to each embolization. This cycle of alternating emergence and ischemic suppression of the evoked response was continued for 1 hour.

At the conclusion of the 60 min ischemic suppression period, animals received no therapy or one of several drug regimens depending upon the group to which they were assigned, as shown in table I. CSERs were then followed for an additional 15–120 min and the percent recovery relative to baseline recorded. Ten animals in Group 1 were not exposed to ischemia. Four animals in this group underwent surgical preparation and the remaining six animals were not exposed to surgery. The brain waters were all tightly clustered whether or not the animals underwent surgery and were accordingly grouped together. All other groups were subjected to 60 min of ischemia. Eleven animals in Group 2, one animal in Group 9, and two animals in Group 11 received no therapy. Other animals were treated as displayed in table I. PGI₂ (prostacyclin, gift of Upjohn Co., Kalamazoo, MI) was made up as a 25 μg/ml solution in 0.1 M Tris-HCL, 0.15 M NaCl pH 8.5 and infused by ice-embedded syringe controlled by a Sage model 355 continuously variable pump. The rate of infusion was chosen to depress mean arterial pressure.

### Table 1 Definition of the Various Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of animals</th>
<th>Duration of recovery (min)</th>
<th>PGI₂ (ng/kg/min)</th>
<th>Indomethacin (4 mg/kg)</th>
<th>Heparin (300 u/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>—</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>60</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>60</td>
<td>90–260</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>60</td>
<td>90–285</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>60</td>
<td>75–340</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>60</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>60</td>
<td>50–200</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
<td>60</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>15</td>
<td>90–150</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>120</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>120</td>
<td>70–240</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Group 1 was not subjected to ischemia. Four dogs in this group underwent surgical preparation; the remaining six animals were not exposed to surgery. All other groups were subjected to 60 min of ischemia.
pressure between 10 and 20 mm Hg. No relationship was noted between the infusion rate of PGI, in the range from 50–340 ng/kg/min and the degree of neuronal recovery. Indomethacin (Indocin® -gift of Merck, Sharp & Dohme, West Point, PA) was prepared shortly before infusion as a 2 mg/ml solution in 0.1 M Tris-HCL, 0.15 M NaCl pH 8.5.

At the conclusion of the recovery period, a 1-min $^{14}$C-iodoantipyrine autoradiographic blood flow study was performed. Essentially, this required intravenous infusion of 50 $\mu$Ci/kg of $^{14}$C-iodoantipyrine at a constant rate over a 1-min period while arterial blood was sampled every 4–6 sec. The cardiac arrest that terminated this procedure was produced by injecting a bolus of 50 cc of saturated potassium chloride through the right femoral vein catheter into the right ventricle. The brain, spinal cord, and heart were then removed, frozen in liquid freon suspended over liquid nitrogen, and cut into 20-micron sections. The tissue concentration of the isotope was determined autoradiographically. Local blood flow was calculated from the following formula:

$$C_i(T) = \lambda k_i \int_0^T C_i e^{-k_i T} dt,$$

where $C_i(T)$ is the concentration of tracer substance in the tissue at time $T$; $\lambda$ is the tissue-blood partition coefficient for the tracer material (approximated as 1); $k_i$ is the rate of blood flow per unit weight of tissue multiplied by the reciprocal of the partition coefficient for that tissue; and $C_i$ is the concentration of tracer substance in the arterial blood.

Determination of Tissue Wet Weight and Dry Weight and Calculation of Percentage Water:

From a 2 mm thick coronal tissue section through sensorimotor cortex in the right hemisphere, two gray matter samples were excised from the superolateral cerebral cortex and two samples of underlying white matter were also obtained. The samples were individually placed in tared, stoppered weighing vials and usually placed in tared, stoppered weighing vials and Drierite®. The tared vials were then reweighed to yield constant weight (as determined in preliminary experiments) in an oven at 110°C for 48 hrs and subsequently brought to room temperature in a dessicant oven Drierite® (calcium sulfate). The tissue samples were dried to constant weight (as determined in preliminary experiments) in an oven at 110°C for 48 hrs and subsequently brought to room temperature in a dessicant oven Drierite®. The tared vials were then reweighed to yield the dry weight. The percentage solids for each sample was calculated:

$$% \text{ solids} = \frac{\text{dry weight of tissue (g)}}{\text{wet weight of tissue (g)}} \times 100$$

The percentage water was determined as:

$$% \text{ water} = 100 - % \text{ solids} = \frac{\text{wet weight} - \text{dry weight}}{\text{wet weight}} \times 100$$

The duplicate determinations for gray matter percentage water were averaged for each animal and the same procedure was followed for white matter.

### Results

Blood gases and body temperature were maintained in the normal range throughout the experiment in all groups. In the embolized groups large enough for statistical analysis (groups 2–8), baseline and final mean arterial blood pressure (MAP) were virtually identical (118 ± 17 mm Hg and 117 ± 2 mm Hg respectively; mean ± SEM): The cerebrospinal fluid pressure (CSFP) underwent a large increase in these same groups after embolization. The mean ± SEM CSFP was 63 ± 9 mm H2O at baseline and rose to 194 ± 15 mm H2O by the conclusion of the experiment.

The mean ± SEM percentage water for gray and white matter, and the corresponding mean ± SEM percentage cortical sensory evoked response (CSER) recovery are shown for each group in table 2. In gray matter, mean percentage brain water was increased in all embolized groups so that 1 h of ischemia in this model produced edema regardless of the type of infusate subsequently administered. By one-way analysis of variance (ANOVA), there was no difference in percentage gray matter water among the embolized groups followed for a one hour recovery period, groups 2–8 ($p > 0.1$). A three-way comparison of percentage gray matter water was made between control animals not subjected to embolization (Group 1), 81.1 ± 0.2 (mean ± SEM), animals receiving effective drug therapy (Group 3), 82.4 ± 0.3, and animals receiving an infusate without therapeutic benefit (Groups 2, 4–8), 82.8 ± 0.2, as shown in table 3. The difference between these groups was significant at $p < 0.001$ by one-way ANOVA. Both the effective therapy group and the ineffectual infusate group differed significantly from controls ($p < 0.01$) but did not differ from each other ($p > 0.1$) by Bonferroni testing.

The mean percentage brain water in white matter of embolized groups was not significantly different than controls (table 2). In correlations of brain edema with other variables, therefore, only associations with gray matter water were analyzed.

<table>
<thead>
<tr>
<th>Group</th>
<th>Percentage water (mean ± SEM)</th>
<th>Percentage recovery CSER</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81.1 ± 0.2</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>83.1 ± 0.4</td>
<td>22 ± 3</td>
</tr>
<tr>
<td>3</td>
<td>82.4 ± 0.3</td>
<td>50 ± 4</td>
</tr>
<tr>
<td>4</td>
<td>83.6 ± 0.6</td>
<td>27 ± 8</td>
</tr>
<tr>
<td>5</td>
<td>81.8 ± 0.6</td>
<td>21 ± 4</td>
</tr>
<tr>
<td>6</td>
<td>81.7 ± 0.8</td>
<td>22 ± 8</td>
</tr>
<tr>
<td>7</td>
<td>83.2 ± 0.2</td>
<td>18 ± 6</td>
</tr>
<tr>
<td>8</td>
<td>82.7 ± 0.5</td>
<td>15 ± 4</td>
</tr>
<tr>
<td>9</td>
<td>82.0</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>83.8</td>
<td>37</td>
</tr>
<tr>
<td>11</td>
<td>82.4 ± 0.4</td>
<td>17 ± 2</td>
</tr>
<tr>
<td>12</td>
<td>85.6 ± 0.6</td>
<td>82 ± 35</td>
</tr>
</tbody>
</table>

### TABLE 2 Tabulation of the Corresponding Mean ± SEM Gray Matter Water, White Matter Water, and Percentage CSER Recovery for Each Group
Table 3  Three-way Comparison of Percentage Gray Matter Water (mean ± SEM) and Associated p-Value by One-way ANOVA and Bonferroni Testing

<table>
<thead>
<tr>
<th>Effective therapy (group 3)</th>
<th>Ineffectual infusate (groups 2 &amp; 4-8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>82.4 ± 0.3</td>
<td>82.7 ± 0.2</td>
</tr>
<tr>
<td>p &lt; 0.01</td>
<td>p &gt; 0.10</td>
</tr>
</tbody>
</table>

No correlation was detected between either MAP or CSFP and percentage brain water in gray matter. When percentage gray matter water in embolized Groups 2-8 were correlated with percentage CSER recovery, no association was found; R = - 0.01, p > 0.10 (fig. 1). Moreover, sorting and recombining embolized animals into an effective therapy group (Group 3) and an ineffectual infusate group (Groups 2, 4-8) and analyzing each of these two groupings separately failed to expose any correlation between amount of brain edema as indicated by percentage gray matter water and the percentage CSER recovery; R = - 0.09, p > 0.10 and R = 0.15, p > 0.10, respectively.

Gray matter blood flow was calculated as an unweighted average from the following structures: auditory cortex, sensorimotor cortex, visual cortex, anterior association cortex, anterior cerebral-middle cerebral watershed cortex, posterior cerebral-middle cerebral watershed cortex, caudate nucleus, thalamus and hippocampus. In embolized animals, gray matter blood flow was 50 ± 33 ml/100 gm/min (mean ± sd). White matter blood flow was 14 ± 7 ml/100 gm/min. White matter blood flow was calculated as an unweighted average from the following structures: anterior centrum ovale, middle centrum ovale, corpus callosum, internal capsule, and optic radiations. There were no significant differences in average gray or white matter blood flow among the various groups. Mean gray matter blood flows measured at the end of the one hour recovery period in embolized animals showed no correlation with percentage gray matter water. However, mean white matter blood flows and, in particular, middle centrum ovale blood flow did inversely correlate with gray matter water; R = - 0.31, p < 0.05 and R = - 0.37, p < 0.02 respectively. This negative correlation was improved when the animals receiving effective therapy (Group 3) were excluded; R = - 0.40, p < 0.02 and R = - 0.49, p < 0.01 respectively.

Embolized animals were sorted into two groups by the presence (n = 9) or absence (n = 38) of “neuron-disabling” flows defined as 15 ml/100 gm/min or less for gray matter and 6 ml/100 gm/min or less for white matter. As depicted in table 4, the CSER percentage recoveries in these two groups were significantly different by Student t-test: “neuron-disabling” flow present — 13.9 ± 2.9% CSER recovery, “neuron-disabling” flow absent — 30.9 ± 2.9% CSER recovery (mean ± SEM), p < 0.01. The two groups did not, however, differ with regard to percentage gray matter water: “neuron-disabling” flow present — 83.1 ±

![Figure 1](http://stroke.ahajournals.org/)

**Figure 1.** A scatter plot of the relationship between percentage gray matter water and corresponding percentage CSER recovery within individual animals comprising Groups 2-8.
The apparent mechanism is a mas­sion of interendothelial junctions in ischemia produced in which tissue perfusion has been interrupted by vessel ligation, increased permeability of the blood brain barrier (BBB) is a relatively late phenomenon occurring after a minimum of 3–4 hr. In contrast, BBB opening is demonstrable in cerebral air embolism after seconds. The increase in permeability to protein-bound tracers does not appear to involve disruption of interendothelial junctions in ischemia produced by vessel ligation. The apparent mechanism is a massive increase in the shunting of the vesicular transepithelial transfer system, “pinocytosis.” Some studies indicate that increased pinocytosis with maintained interendothelial integrity is also the mechanism of permeability increase in cerebral air embolism but other work suggests that disruption of interendothelial junctions with endothelial cell desquamation can occur in this condition. Mediators of accelerated pinocytosis include serotonin and calcium.

An increase in tissue water could be expected to increase local tissue pressure and cause a corresponding decrease in local perfusion pressure. This should have been reflected in a mild to moderate decrease in local blood flow provided other factors remained unchanged. Some correlation was noted between white matter blood flow (particularly middle centrum ovale) and percentage gray matter water in embolized animals followed for a one hour recovery period and the association was tightened when animals receiving effective therapy were eliminated from consideration. The absence of correlation between gray matter water and gray matter blood flow in this series is unexplained. As previously described, no correlation was noted between average gray or white matter blood flow and CSER recovery. However, separation of the animals into two groups based on the presence or absence of “neuron-disabling” blood flows did produce corresponding CSER recoveries which differed significantly, as depicted in Table 4. Despite the different CSER recoveries in these two groups, the amount of edema as indicated by percentage gray matter water did not differ significantly. Instead, both groups had gray matter water percentages that were increased with respect to controls. In this study, then, neuronal recovery as indicated by the CSER is related to the presence or absence of “neuron-disabling” flows but the percentage CSER recovery did not correlate with the presence or degree of gray matter edema and increased gray matter water occurred in all previously ischemic animals with and without “neuron-disabling” flows as measured at the end of the recovery period.

If the local increase in tissue fluid that constitutes circumscribed edema causes neuronal damage or exacerbates existing damage, one would expect a strong negative correlation between brain water content and a quantifiable index of neuronal function such as the CSER percentage recovery. Further, the presence of brain edema should contribute to poor recovery regardless of whether therapy was given and effective therapy should produce a concomitant decrease in cerebral edema. These consequences of the hypothesis, “circumscribed edema per se causes neuronal damage or exacerbates existing damage” being true are not observed in the present study. It would appear, then, that in reversible focal ischemia, a degree of cerebral edema such as that observed in this study is not a good predictor of the degree of post-ischemic neuronal recovery. This does not, of course, exclude the possibility that edema exceeding some higher threshold of severity would correlate better with neuronal recovery. An alternative possibility is that brain ischemia engenders two parallel processes which are not necessar-
ily tightly coupled. Ischemia creates the metabolic conditions that provoke an increased cellular imbibition of water, and produces a state of increased vascular leakiness through stimulation of pinocytosis and also, perhaps, through disruption of interendothelial junction integrity. These perturbations lead to an increase in brain tissue water. Concomitantly, parenchymal metabolic derangements (some of which cause tissue fluid accumulation) and a multifactorial interaction at the blood-endothelial interface (of which some components cause tissue fluid accumulation) develop which have a direct influence on neuronal function and recovery. A particularly thorough and lucid description of the parenchymal metabolic derangements has appeared in a recent speculative review.

Events at the blood-endothelial interface are not fully characterized and have been designated "blood-damaged tissue interaction." Inferences by Stewart et al. provide a link between increased vessel permeability and activation of soluble and cellular systems in blood. The increased permeability of the endothelium would permit access of contact-activated proteins such as Factor XII to subendothelial collagen with consequent activation of the myriad blood responses. Factor XII is an 80,000 mw protein which binds to negatively charged surfaces, undergoes a change in conformation and becomes susceptible to serine proteases such as kallikrein. As a result of limited proteolytic cleavage of a single bond, activated factor XII (HFa) is formed without reduction in molecular weight. HFa can activate the intrinsic coagulation pathway, generate the fibrinolytic enzyme plasmin and lead to formation of bradykinin. HFa can be further attacked by kallikrein to form a 28,000 mw Hageman factor fragment (HFf). Formation of this molecule can result in generation of kallikrein, plasmin, bradykinin, and activation of the classical complement pathway by hydrolysis of C1. A hypothetical schematization of some of the events in "blood-damaged tissue interaction" is shown in figure 2. Data from allied fields support this systems diagram of the elements potentially involved. Essentially, the process can be envisioned as an interwoven fabric of soluble biochemical factors and cellular systems which relate in a complex, often cybernetic fashion. Regulatory proteins control the spread of activation along potential pathways and it remains for future research to identify the major participating systems and to gauge the relative contribution of each. The net effect of these processes over time is regarded as a progressive increase in resistance in the microvessels of the injury zone with consequent focal shut-down of nutrient flow.

---

**Figure 2.** A systems diagram depicting hypothetical vessel changes and the multifactorial blood response that may occur in a zone of acute CNS injury. Such a process of "blood-damaged tissue interaction" could cause both the accumulation of edema and microcirculatory shut-down within injury zone. \( \alpha_2M = \alpha_2 \text{macroglobulin}; \ AT \ III = \alpha_2 \text{antithrombin III}; \ CIINH = \text{CI esterase inhibitor}; \ a_2 \text{AP} = \alpha_2 \text{antiplasmin}. \)
focal brain ischemia, flow rates in a critical range may cause abeyance of neurologic function, the "ischemic penumbra" but not proceed rapidly to infarction. Progressive stanching of nutrient flow in the injury zone through a process of "blood-damaged tissue interaction" that is measured in hours rather than minutes could convert functionally impaired but viable neurons to an infarct. This holds out the prospect of specific emergency medical intervention designed to sustain microcirculatory perfusion in the injury zone. The importance of considering the multifactorial network proposed as "blood-damaged tissue interaction" is that if such processes are operative, curbing them could be achieved only by interfering with activity of agonists or enhancing activity of inhibitors at multiple sites; measures that block single components of the network would tend to be circumvented.

A zone of CNS tissue in the "ischemic penumbra" is probably in a metastable state so that progressive metabolic derangements and "blood-damaged tissue interaction" emerge, convert the lesion to a state of irretrievable damage. As the molecular details of the tissue metabolic perturbations and "blood-damaged tissue interaction" emerge, they ought to suggest effective new therapeutic measures for the acute phase of CNS ischemia.

Acknowledgments
Naval Medical Research and Development Command, Research Task No. M0099PN0011.050. The opinions and assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large. The experiments reported herein were conducted according to the principles set forth in the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Resources, National Research Council, DHEW, Pub. No. (NIH) 7823. The authors gratefully acknowledge the technical assistance of Messrs. J. A. Miles, Jr., G. E. Sloan, J. R. De Jesus, J. F. Greenbeck, Mrs. C. B. Jones, Messrs. P. A. Babb, M. A. Byers, J. M. Bertocnini, and Ms. R. A. Seifert. Also acknowledged is the editorial assistance of Ms. R. A. Balenger. We wish to thank the Upjohn Company, Kalamazoo, MI and Merck, Sharp & Dohme, West Point, PA, for supplying drugs used in this study. Karen D. Pettigrew, Ph.D., National Institute of Mental Health, N.I.H., provided consultation regarding statistical analysis.

References
34. Wolfe LS: Eicosanoids: Prostaglandins, thromboxanes, leuko-

A Comparison of Trends in Mortality from Stroke in the United States and Rochester, Minnesota

GREGORY L. ANDERSON, M.D. AND JACK P. WHISNANT, M.D.

SUMMARY More uniform methods of diagnosis and determination of the cause of death result in greater reliability of trends in mortality from stroke. In all categories of stroke except subarachnoid hemorrhage, the mortality rates in Rochester, Minnesota, are lower and show a more rapid decline with time than in the United States as a whole. The differential between the rates for United States white population and the Rochester population is most evident in the older age groups. This difference may be due to the effects of revisions in the International Classification of Diseases and/or to the assignment of nonstroke deaths to stroke causes in the United States as a whole to a greater extent than in Rochester. Whether different patterns of medical care affect the trends in stroke mortality has not been determined. The trends in mortality from various categories of stroke in Rochester are reliable because some of the inconsistencies of diagnosis, assignment of cause of death, and coding changes have been overcome. The decline in mortality rates for Rochester corresponds well with decreasing incidence rates and lack of change in case fatality rates previously reported.

A DECLINE IN THE MORTALITY from cerebrovascular disease during the last several decades has been described in several reports. However, there are inherent difficulties in the interpretation of mortality data. Problems that can be identified include revisions in codes for cause of death, changes in terminology and patterns of diagnosis, low autopsy rates, and low accuracy of diagnosis, especially in differentiating various categories of cerebrovascular disease.

This study was undertaken to examine the trends in mortality from stroke in Minnesota and the United States white population and to compare these with the trends in mortality from stroke in the community of Rochester, Minnesota. In Rochester, virtually all residents receive their medical care at the Mayo Clinic and its associated hospitals or the Olmsted Medical Group and the Olmsted Community Hospital. The records of all of these facilities are linked for indexing and retrieval. This assures identification of practically all residents with serious medical problems, whether their conditions were diagnosed in the hospital or in one of the outpatient facilities or at autopsy. The community has long had a high degree of neurologic expertise, a high autopsy rate (> 50%), and a relatively uniform assignment of cause of death. Virtually all death certificates, including those for deaths in which no autopsy is performed, are completed by Mayo Clinic pathologists.

Methods

All patients were identified who had a clinical or pathologic diagnosis of stroke at some time and died while residents of Rochester during the 30-year period 1945–1974. For the purpose of this study, the criteria for the diagnosis of stroke included (1) signs of focal neurologic deficit due to a vascular lesion of the central nervous system present for at least 24 hours and clinical characteristics to suggest that a stroke was the cause of the lesion or (2) a recent stroke documented at autopsy. Patients with transient ischemic attacks — focal cerebral ischemia of less than 24 hours duration — were not included.

Death certificates for all patients were reviewed for the date of death, confirmation of Rochester residency (regardless of whether the patient was actually in the city at the time of death), presence of any category of
The amount of circumscribed brain edema and the degree of post-ischemic neuronal recovery do not correlate well.

J M Hallenbeck, D R Leitch, A J Dutka and L J Greenbaum, Jr

Stroke. 1982;13:797-804
doi: 10.1161/01.STR.13.6.797

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/13/6/797

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/